



Natalie Long, MD;
Liz Nguyen, MD; James
Stevermer, MD, MSPH
Department of Family and
Community Medicine,
University of Missouri-
Columbia (Drs. Long and
Stevermer); University of
Chicago, Department of
Family Medicine
(Dr. Nguyen)

DEPUTY EDITOR

Anne Mounsey, MD
Department of Family
Medicine, University of
North Carolina at Chapel
Hill

It's time to reconsider early-morning testosterone tests

Guidelines recommend collecting an early-morning sample to compensate for the natural diurnal variation in testosterone levels. But for men 45 and older, this is unnecessary.

PRACTICE CHANGER

Early-morning testosterone tests are necessary only for men younger than age 45. Because the natural diurnal variation in testosterone levels tends to diminish with age, it is acceptable to test men ages 45 and older before 2 pm.¹

STRENGTH OF RECOMMENDATION

B: Based on a retrospective cohort study.

Welliver RC Jr, Wiser HJ, Brannigan RE, et al. Validity of midday total testosterone levels in older men with erectile dysfunction. *J Urol*. 2014;192:165-169.

ILLUSTRATIVE CASE

It's noon, you are finishing up a visit with a 62-year-old man with erectile dysfunction (ED), and you want to evaluate for androgen deficiency. Should you ask him to return for an early-morning visit so you can test his testosterone level?

Increasing public awareness of androgen deficiency has led to more men being tested for testosterone levels. Current Endocrine Society guidelines recommend against routine screening for androgen deficiency in men who do not have symptoms.² However, for men with classic symptoms of androgen deficiency—such as decreased libido, ED, infertility, depression, osteoporosis, loss of secondary sexual characteristics, or reduced muscle bulk or strength—measurement of total testosterone level is recommended.²

Due to the natural diurnal variation in serum testosterone levels, the guidelines recommend collecting the sample in the early morning.² This recommendation is based on small observational studies that included men mostly younger than 45 years of age that found a significant difference in testosterone levels between samples drawn early in the morning and in the afternoon.³⁻⁵

In recent years, several studies have indicated that this variation declines as men age.⁴⁻⁶ Recently, researchers evaluated the effects of age and time of testing on men's total testosterone levels.

STUDY SUMMARY

Differences in testosterone levels are significant only in younger men

Welliver et al¹ performed a retrospective chart review of 2569 men seen at a Minneapolis Veterans Affairs hospital for ED who had total testosterone levels measured between 7 am and 2 pm over a 15-year period. Men whose total testosterone levels were outside the normal range (>1000 or <50 ng/dL) or who had total testosterone drawn after 2 pm were excluded. The authors analyzed the results based on age, creating one group for men ages <40 years and 5-year age groups for all other men. Using scatterplot techniques, they separated each age group into 2 subgroups based on draw times—7 am to 9 am, or 9 am to

2 pm—and compared the mean total testosterone level for each age and time.

The participants' mean age was 63 years. Younger men (<45 years) had the largest variation in serum total testosterone, with a large and significant decrease after 9 am. Only the youngest 2 groups (ages <40 and 40-44 years) showed a large decrease in total testosterone in specimens collected after 9 am compared to those drawn between 7 am and 9 am (mean difference 207 and 149 ng/dL, respectively). This variation was not observed in patients over age 45. Although there was a statistically significant difference between early and later testosterone levels in men ages 70 to 74 years, the absolute difference—34 ng/dL (452 vs 418 ng/dL)—was unlikely to be clinically significant.

WHAT'S NEW

For older men, later testing will not affect results

This study confirms previous research showing that the diurnal effect on testosterone levels becomes blunted with increasing age, at least in this group of men with ED. Allowing older men to have total testosterone levels drawn until 2 pm would allow for greater patient flexibility in draw times with little change in results.

CAVEATS

Study's methodology cannot account for several potential confounders

This retrospective study analyzed only a single random testosterone level measurement from each participant, rather than repeat testosterone levels over the course of a day. However, the study was large (2569 men) and it used mean values, which should at least partially mitigate the effect of having only a single level from each participant.

The study measured total testosterone and did not account for potential confounding factors—such as obesity or use of testosterone replacement therapy or androgen deprivation therapy—that could affect sex-hormone binding globulin, thus potentially altering total testosterone level. However, the authors estimated that less than 2% of the entire cohort were likely to have unrecognized

hormonal manipulation with exogenous gonadotropins.

All of the men in the study were seen for ED, and it could be that men with ED have more flattening of the diurnal variation than men without ED; however, we are unaware of other data that support this.

Up to 30% of men who have an early-morning testosterone level that is low may have a normal result when testing is repeated.^{2,5} Therefore, for all men who have low testosterone level test results, draw a repeat total testosterone level before 9 am to confirm the diagnosis. Also, this study did not evaluate the course of testosterone levels throughout the later afternoon and evening, and it remains unclear whether levels can be drawn even later in the day.

CHALLENGES TO IMPLEMENTATION

Your lab's policies might require early-morning draws

There will probably be few barriers to implementing this change, unless local laboratory policies are inflexible regarding the timing of testosterone draws. **JFP**

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References

1. Welliver RC Jr, Wiser HJ, Brannigan RE, et al. Validity of midday total testosterone levels in older men with erectile dysfunction. *J Urol*. 2014;192:165-169.
2. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536-2559.
3. Cooke RR, McIntosh JE, McIntosh RP. Circadian variation in serum free and non-SHBG-bound testosterone in normal men: measurements, and simulation using a mass action model. *Clin Endocrinol (Oxf)*. 1993;39:163-171.
4. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab*. 1983;56:1278-1281.
5. Brambilla DJ, Matsumoto AM, Araujo AB, et al. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab*. 2009;94:907-913.
6. Crawford ED, Barqawi AB, O'Donnell C, et al. The association of time of day and serum testosterone concentration in a large screening population. *BJU Int*. 2007;100:509-513.



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